55. A method of claim 54 wherein the active enamel substance comprises amelogenins and has a molecular weight of about 60 kDa to about 120 kDa as determined by SDS Page electrophoresis.

56. A method for treating epidermally derived cancers and tumors, the method comprising administering topically to a mammal in need thereof a therapeutically effective amount of an active enamel substance.

57. A method of claim 56 wherein the active enamel substance comprises amelogenins and has a molecular weight of about 60 kDa to about 120 kDa as determined by SDS Page electrophoresis.

REMARKS

Claim 28 was amended and new claims 47-57 have been added. No new matter has been added by virtue of the within amendment, support therefor being found throughout the specification and the original claims of the application.

Applicants also submit that these amendments may be properly entered at this time, i.e., after final rejection pursuant to 37 C.F.R. §1.116, because the amendments do not raise any new issues or require a new search and they reduce the issues for appeal.

Further, entry of the within amendments also is proper in that the amended claims are within the scope of prior searches. For example, claim 28 has been amended to provide for the treatment of semi-malignant neoplasms (in addition to benign or malignant); support therefor can be found, e.g., in the specification at page 4, lines 26-30. New claim 47 recites a particularly preferred embodiment of the invention wherein the active enamel substance comprises amelogenins and has a molecular weight between 60 and 120 kDa, e.g., consistent with the active enamel substance commercially known as EMDOGAIN or EMD. New claims 48-57 each relate to the treatment of ectodermally or epidermally derived neoplasms, neoplastic cells,

cancers and tumors. Support for these particular claims can be found throughout the specification. (See, in particular, the application at page 4, line 21 to page 5, line 31, and Table 1 appearing on page 26.) Accordingly, entry of the within amendments is earnestly solicited.

As an initial matter, Applicants thank Examiner Harris for the time and courtesy extended to the undersigned attorneys on June 10, 2002, during their telephonic interview. During such interview, the remaining rejections were discussed in detail, as were possible ways to overcome the rejections.

Turning now to the Office Action, claims 28-46 stand rejected under 35 USC §112, first paragraph. As the rejection is understood, the position is taken that while the specification is enabling for a method for treating malignant cancer cell lines (such as those listed in Table 1 of the present application), the specification is allegedly non-enabling for a method for preventing or treating malignant or benign neoplasms as presently claimed.

The rejection is traversed.

Attention is drawn to the present application at page 4, line 35 to page 5, line 31, wherein the topical application of an active enamel substance to a suitable surface at or on affected tissue is clearly described. Such description is provided in sufficient detail to render a person skilled in the art able to practice and implement such treatment commensurate in scope with the claimed invention without undue experimentation.

The application further includes numerous working examples which demonstrate the invention. In view of such extensive disclosure, the skilled worker clearly would be able to practice the invention, commensurate with that claimed.

Moreover, independent claim 28 recites a method for treating *epithelially derived* benign, semi-malignant or malignant neoplasms which comprises *administering topically* to a mammal in need thereof a therapeutically effective amount of an *active enamel substance*. Similarly,

newly presented independent claims 48 and 52 are each directed to methods for treating *ectodermally derived* neoplasms or neoplastic cells which comprises *administering topically* to a mammal in need thereof a therapeutically effective amount of an *active enamel substance.* The scope of such claims does not include *all benign or malignant neoplasms*, as appears to be contended in the Office Action.

Still further, Table 1 shows data relative to use of the present invention in ten (10) different cell lines, originating from five (5) different species of tissue (glandular, bone, skin, ovarian and muscle). Each of the cancers exemplified by the cell lines treated and listed in Table 1 are *ectodermally derived*; certain of the cancers which are ectodermally derived also are *epithelially or epidermally derived.* As such, it is respectfully submitted that such data along with the supporting specification provides ample enabling disclosure for the present invention as claimed.

In another aspect of the enablement rejection, the Office Action questions the adequacy of the control data provided in the specification in that there is no evidence presented as to the treatment of normal cell line counterparts. In particular, the Office Action states that while Applicants have included HeLa cells that have not been treated with EMD, there are no experiments presented implementing the non-cancerous cell types.

Applicants note that it is not possible to provide the type of control experiments suggested in the Office Action, e.g., treatment with an active enamel substance such as Emdogain on untransformed epithelial cells. First, Emdogain will most likely have a negative effect on untransformed epithelial cells, meaning a suppressive effect on proliferation, migration and attachment, as compared to its growth-promoting effect on normal fibroblasts. Moreover, Emdogain selectively suppresses epithelial cell growth and migration. For that reason, Emdogain is preferably applied topically on the epithelially derived neoplasm. Indeed, it would not be advisable in accordance with the present invention to introduce Emdogain systemically into the patient's body. Such an administration would most likely have a negative effect on

other, non-cancerous epithelial cells. Published studies support Applicants' assertion and have reported that Emdogain does not spread into neighboring tissue.

Further, adequate and pertinent control data is provided in the specification. For example, certain experiments were performed to investigate whether or not active enamel substances could reduce epithelial cancer cell growth. Thus, the controls chosen in the present application were untreated HeLa cells versus treated HeLa cells (see the present application at page 23, lines 17-18).

Moreover, the present invention addresses the technical problem of the risk of transformed cells migrating from the site of a removed epithelially derived tumor or neoplastic tissue and the recurrence of said tumor or neoplastic tissue after surgery (see the present application at page 5, lines 16-27). As described above, the active enamel substance of the invention will drastically reduce the risk of migration or recurrence of the removed epithelially derived tumor or neoplasm when administered topically. Indeed, this is testament to the present invention's surprising capability of selectively reducing the growth of epithelially and ectodermally derived cancer cells.

Experimental controls were performed in Examples 2 and 3 of the present application. Such controls are clearly disclosed in the application and the results for such controls shown. (See page 23, lines 17-19, page 25, lines 6-7 and Figures 1-3 of the application.) In Example 2, HeLa cells cultured under similar conditions in the absence of EMD are used as controls and the results are shown in parallel, whereas the results of the cultures in Example 3 are presented as the ratio between EMD treated cells and untreated cells.

Still further, the Office Action raises a question as to which substances should be considered derivatives capable of inducing apoptosis. For example, the Office Action asks whether enamel substances, such as proline-rich non-amelogenins and tuftelins, could be expected to act in the same manner yielding the same result.

It is respectfully submitted that the specification provides ample enabling disclosure with respect to this aspect of the invention, and would be readily understood by the skilled worker. In particular, attention is directed to the present application at page 7, line 1 to page 9, line 7, wherein several examples of suitable proteins for use in accordance with the present invention are described with particularity. Additionally, note the application at page 7, lines 10-15, where it is stated that amelogenins constitute about 90% w/w of the matrix proteins, with the remaining 10% including proline-rich non-amelogenins, tuftelins, tuft proteins, etc.

In view of the arguments set forth above, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, are thus requested.

Claims 28-46 stand rejected under 35 USC §112, second paragraph, on the grounds that such claims are allegedly rendered vague and indefinite due to the use of several objectionable terms.

The rejection is traversed.

Applicants submit that the noted claims are abundantly clear and definite when read in view of the supporting specification, as is proper.

For example, the Office Action objects to use of the terms "enamel substance" and "active enamel substance" as those terms appear in the claims. Similarly, the Office Action objects to the term "derivatives", "derivatives thereof" and "mixtures thereof" as they appear in the noted claims.

It is respectfully submitted that such terms are clearly defined in the present application. As such, they would be readily understood by the skilled artisan as clearly defining the metes and bounds of the noted claims.

See, for example, the application at page 1, lines 25-32, where the term "active enamel substance" is defined as a collective term for enamel matrix, enamel matrix derivatives and/or enamel matrix proteins. Additional relevant disclosure concerning these substances is provided beginning at page 5, line 33 to page 10, line 7 of the present application. Particular attention is directed to page 7, lines 1-8 where examples of proteins suitable for use according to the invention are described.

With respect to the terms "derivatives", "derivatives thereof" and "mixtures thereof" as used in the context of enamel matrix derivates and mixtures, attention is directed to the disclosure at page 7, lines 21-27. That passage clearly describes derivatives and mixtures of the group consisting of enamelins, amelogenins, non-amelogenins, proline-rich non-amelogenins, amelins, tuftelins. Additionally, see in particular, the application at page 7, line 10 where the statement is made that: "In general, the major proteins of an enamel matrix are known as amelogenins. They constitute about 90% w/w of the matrix proteins. The remaining 10% w/w includes proline-rich non-amelogenins, tuftelin, tuft proteins, serum proteins and at least one salivary protein...." A description of other protein substances suitable for use according to the present invention is provided beginning at page 7, line 21.

Still further, attention is directed to text beginning at page 7, line 32 which indicates that epithelial cells associated with ameloblasts are believed to be induced to undergo apoptosis by degradation products migrating from the enamel matrix during dental enamel development. The application goes on to state that such degradation products, which generally have a molecular weight between about 3kDa and 25 kDa, such as between 5kDa and 20 kDa, may be particularly effective for use according to the present invention.

In view of such disclosure, it is respectfully submitted that the noted claims would be abundantly clear to those skilled in the art.

Reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, are requested.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES

Claim 28 was amended as follows.

28. A method for treating [of] epithelially derived [malignant or] benign, semi-malignant or malignant neoplasms, the method comprising administering topically to a mammal in need thereof a therapeutically effective amount of an active enamel substance.

New claims 47-57 were added.

47. A method of claim 28 wherein the active enamel substance comprises amelogenins and has a molecular weight of about 60 kDa to about 120 kDa as determined by SDS Page electrophoresis.

48. A method for treating ectodermally derived benign, semi-malignant or malignant neoplasms, the method comprising administering topically to a mammal in need thereof a therapeutically effective amount of an active enamel substance.

49. A method of claim 48 wherein the ectodermally derived neoplasms are epithelially derived neoplasms.

50. A method of claim 48 or 49 wherein the active enamel substance comprises amelogenins and has a molecular weight of about 60 kDa to about 120 kDa as determined by SDS Page electrophoresis

51. A method of claim 48 wherein the ectodermally derived benign, semi-malignant or malignant neoplasms originate in a bodily tissue selected from the group consisting of glandular, bone, skin, ovarian and muscle tissue.

52. A method for treating conditions in a mammal characterized by the occurrence of ectodermally derived neoplastic cells, the method comprising administering topically to a mammal in need thereof a therapeutically effective amount of an active enamel substance.

53. A method of claim 52 wherein the active enamel substance comprises amelogenins and has a molecular weight of about 60 kDa to about 120 kDa as determined by SDS Page electrophoresis.

54. A method for treating ectodermally derived cancers and tumors, the method comprising administering topically to a mammal in need thereof a therapeutically effective amount of an active enamel substance.

55. A method of claim 54 wherein the active enamel substance comprises amelogenins and has a molecular weight of about 60 kDa to about 120 kDa as determined by SDS Page electrophoresis.

56. A method for treating epidermally derived cancers and tumors, the method comprising administering topically to a mammal in need thereof a therapeutically effective amount of an active enamel substance.

57. A method of claim 56 wherein the active enamel substance comprises amelogenins and has a molecular weight of about 60 kDa to about 120 kDa as determined by SDS Page electrophoresis.